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CONTROLLED DRUG RELEASE ASYMPTOTICS*

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Abstract. The solution of Higushi's model for controlled release of drugs is examined when the solubility of the drug in the polymer matrix is a prescribed function of time. A time-dependent solubility results either from an external control or from a change in pH due to the activation of pH immobilized enzymes. The model is described as a one-phase moving boundary problem which cannot be solved exactly. We consider two limits of our problem. The first limit considers a solubility much smaller than the initial loading of the drug. This limit leads to a pseudo-steady-state approximation of the diffusion equation and has been widely used when the solubility is constant. The second limit considers a solubility close to the initial loading of the drug. It requires a boundary layer analysis and has never been explored before. We obtain simple analytical expressions for the release rate which exhibits the effect of the time-dependent solubility.

Key words. moving boundary problem, boundary layer, exponentially small asymptotics, controlled drug release, nonlinear diffusion

AMS subject classifications. 35R35, 35B25, 35C20, 58G18, 80A22, 35C15, 35K60, 73F15, 76R99

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1. Introduction.

The main objective of a controlled release system is to deliver a drug at a predetermined rate and for an extended period of time [1]. The most common release mechanism is diffusion through a polymeric system. The drug is uniformly distributed in a polymeric matrix or is surrounded by a film. Exposed to environmental fluid, the drug inside the polymeric device is gradually dissolved and then released outward. The drug may be delivered at a constant level whether the body needs it or not. For some drugs, a pattern of input could be more appropriate. For example, a modulated delivery system controlled by external means is known to improve the release pattern of insulin. An even better approach for an optimal delivery system is to design a polymer-drug device so that the drug is released in response to physiological constraints. Polymer-drug matrices containing pH-dependent immobilized enzymes are particularly promising because changes in pH cause dramatic shifts in the solubility of polypeptide drugs [2], [3]. Several systems are developed and tested today for the release of insulin in the presence of excess glucose.

Drug delivery systems activated by external means or responding to a specific agent have in common the fact that a time-dependent feedback is used to control diffusion. The problem is then no longer a simple diffusion problem because the concentration at the boundaries is time dependent and the position of the moving interface between dissolved and loaded drug becomes one of the unknowns of the problem (Figure 1). If the concentration at the boundaries is time independent, Higushi [4], [5] formulated a one-phase moving boundary problem for the diffusion of

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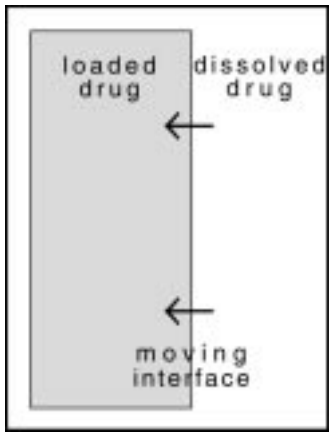

FIG. 1. *Controlled release polymeric device. The release rate of the dissolved drug depends on the time history of the moving interface.*

the dissolved drug in a polymer. The problem was later solved exactly [6]. Lee [7] compared the exact solution and approximate solutions obtained by different methods (pseudo-steady-state approximation, Goodman's integral method). His idea was that some of these methods could be useful for more complicated problems which do not allow an exact solution. This is the case for swelling polymers [8], [9] which exhibit a change in volume or for pH-sensitive polymers [10], [11]. This motivates the study of new asymptotic approximations of the solution of the moving boundary problem. The pseudo-steady-state approximation is easy to apply and is valid if the initial loading of the drug is much larger than its solubility. However, this is not always the case in practical situations. In this paper, we explore a different asymptotic limit, namely, the case of an initial loading close to its solubility. The moving boundary problem is mathematically interesting because it exhibits a boundary layer near the fixed boundary.

The plan of this paper is as follows. In section 2, we formulate Higushi's model and analyze its exact solution for a constant solubility. In section 3, we consider the case of an initial loading of the drug much larger than its solubility. This case leads to the pseudo-steady-state approximation as the leading term of a regular perturbation analysis. The analysis is simple and we summarize the main results for a time-dependent solubility. In section 4, we investigate the case of an initial loading of the drug slightly larger than its solubility. The asymptotic problem is difficult and we give more details. Finally, in section 5, we discuss the relevance of our asymptotic analysis for more complicated problems.

2. Formulation and constant solubility. A drug or bioactive agent is initially immobilized in a polymer matrix. In contact with a dissolution medium (e.g., water or a biological fluid), the drug diffuses through the polymer. See Figure 2. The problem is formulated as a moving boundary problem for the concentration C of the drug [6], [7]. Specifically, C satisfies Fick's equation

$$C_T = DC_{XX} \tag{1}$$

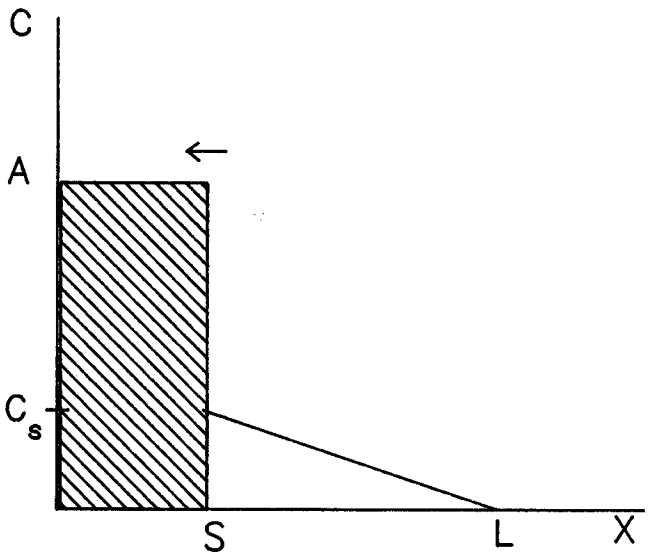

FIG. 2. *One-phase moving boundary problem. C is represented as a function of X when the initial loading of the drug A is much larger than its solubility C_s. The concentration changes linearly from C_s (at $X = S$) to 0 (at $X = L$).*

in the domain $S(T) < X < L$ subject to the following boundary conditions. First, we assume a perfect sink at the fixed boundary which implies the condition

$$C = 0 \text{ at } X = L. \tag{2}$$

Second, C equals the solute solubility at the moving front

$$C = C_s(T) \text{ at } X = S(T). \tag{3}$$

We write $C_s(T) = C_{sm}F(T)$ where C_{sm} is defined as the maximum solute solubility of the drug in the polymer and $0 < F(T) \leq 1$ is a prescribed function of T. Finally, we need a mass balance equation at the moving front since C changes from A to $C_s(T)$. A is defined as the initial loading of the drug. Thus,

$$-DC_X = (C_s(T) - A)\, S'(T) \text{ at } X = S(T). \tag{4}$$

The initial condition for the moving front is $S(0) = L$. With the solution of (1)–(4), we may then determine the release rate defined by

$$R \equiv -DC_X|_{X=L}. \tag{5}$$

If $F = 1$ ($C_s = C_{sm}$), it is well known [6], [7] that the problem (1)–(4) admits an exact solution. This solution will be instructive for our subsequent analysis if A remains close to $C_s(T)$ and its expression is shown in the Appendix. Because the asymptotic properties of this solution that we need have never been examined in the past, we give some details. The position S of the moving front follows a simple $\sqrt{T}$ history given by

$$L - S = \sqrt{2D\alpha T}, \tag{6}$$

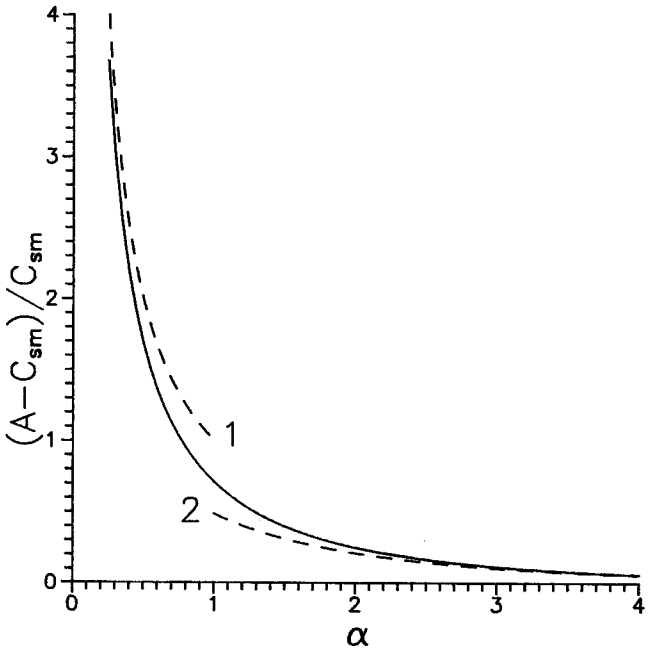

FIG. 3. *Constant solubility. The figure represents* $(A - C_{sm})/C_{sm}$ *as a function of* α *and is given by* (7). *The dotted lines represent asymptotic limits of the function. Lines* 1 *and* 2 *correspond to the limits* $\alpha \to 0$ *and* $\alpha \to \infty$, *respectively, and are given by* (8) *and* (9), *respectively.*

where the constant α is determined implicitly from

$$\frac{A - C_{sm}}{C_{sm}} = \sqrt{\frac{2}{\pi\alpha}} \exp(-\alpha/2) \frac{1}{erf\left(\sqrt{\alpha/2}\right)}. \tag{7}$$

Here $erf(x)$ is the error function [14]. The function (7) is plotted in Figure 3 and exhibits two interesting limits depending on C_{sm} and A. First, the limit $\alpha \to 0$ gives

$$\frac{A - C_{sm}}{C_{sm}} \simeq \frac{1}{\alpha} \tag{8}$$

or, equivalently, $\alpha \simeq C_{sm}/A$ as $C_{sm}/A \to 0$. This is the result of the pseudo-steady-state approximation valid if A is much larger than C_{sm}. Second, the limit $\alpha \to \infty$ gives

$$\frac{A - C_{sm}}{C_{sm}} \simeq \sqrt{\frac{2}{\pi\alpha}} \exp(-\alpha/2), \tag{9}$$

which implies that $C_{sm} \simeq A$. The exponential relation between $A - C_{sm}$ and α reveals that the case $A - C_{sm} \to 0$ is not a regular perturbation problem as in the case of the pseudo-steady-state approximation. A second useful observation is the behavior of the solution in this limit. From (50), we find

$$C \simeq C_{sm} erf\left(\sqrt{\frac{\alpha}{2}}\left(\frac{L - X}{L - S}\right)\right), \tag{10}$$

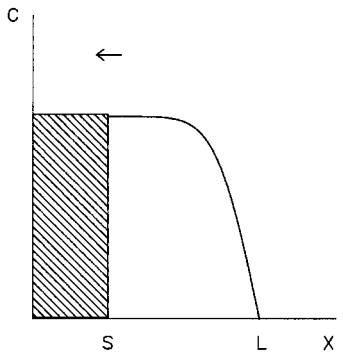

FIG. 4. *One-phase moving boundary problem. C is represented as a function of X when the initial loading A is close to its solubility C_s. The concentration is almost constant but changes rapidly near the fixed boundary at $X = L$.*

which is almost constant ($C \simeq C_{sm}$) in the domain $S \leq X < L$ except in an $O(\alpha^{-1/2})$ boundary layer at $X = L$. See Figure 4.

3. Variable solubility and pseudo-steady-state approximation. In this section, we briefly apply the pseudo-steady-state approximation. To this end, we introduce the following dimensionless variables and parameters:

$$u \equiv C/C_{sm},\ t \equiv \left[DC_{sm}/(AL^2)\right] T,\ x \equiv X/L,\ s \equiv S/L. \tag{11}$$

Using (11), we rewrite (1)–(4) as

$$\epsilon u_t = u_{xx},\ s(t) < x < 1, \tag{12}$$

$$u = 0 \text{ at } x = 1, \tag{13}$$

$$u = f(t) \text{ and } u_x = (1 - \epsilon f(t))\, s'(t) \text{ at } x = s(t),\ s(0) = 1, \tag{14}$$

where

$$\epsilon \equiv C_{sm}/A \text{ and } f(t) \equiv F(T). \tag{15}$$

The pseudo-steady-state approximation is based on the limit $\epsilon \to 0$. The leading approximation is obtained by setting $\epsilon = 0$ in (12)–(14). Integrating the resulting equation for u and applying the two boundary conditions give

$$u = f(t)\frac{x-1}{s-1} + O(\epsilon) \tag{16}$$

and

$$s - 1 = -\sqrt{2\int_0^t f(t')dt'} + O(\epsilon). \tag{17}$$

Note that $s > 0$ restricts the time interval. Using (5), we determine the release rate R given by

$$R = -D\frac{C_s(T)}{S-L} = \sqrt{DAC_{sm}}\frac{F(T)}{\sqrt{2\int_0^T F(T')dT'}}. \tag{18}$$

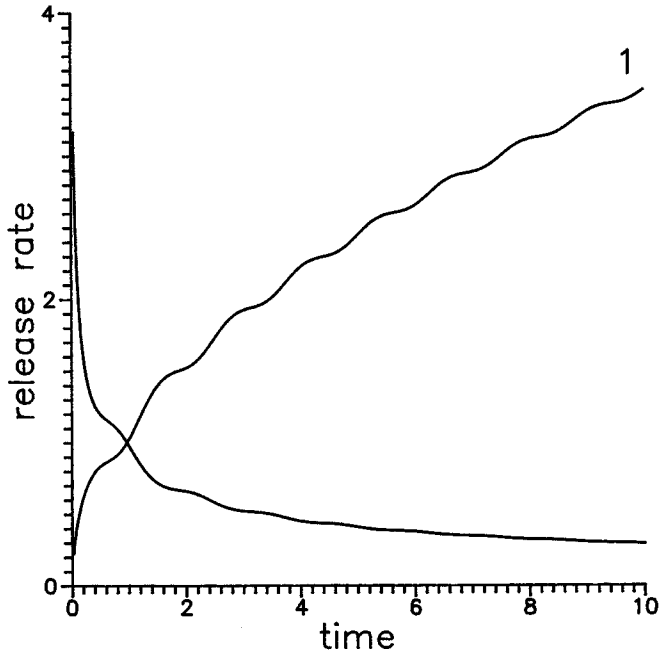

FIG. 5. *Release rate. The figure represents the release rate R divided by $\sqrt{DAC_{sm}}$ as a function of time T. The solution is given by* (20). *The values of the parameters are $b = 0.4$ and $\omega = 5$. Line* 1 *represents the deviation $L - S$ divided by $\sqrt{DC_{sm}/A}$ given by* (17).

For example, if

$$F(T) = 1 - b + b\cos(\omega T) > 0 \ (b < 1/2) \tag{19}$$

is a periodic function of T, R is given by

$$R = \sqrt{DAC_{sm}}\frac{1 - b + b\cos(\omega T)}{\sqrt{2\left((1-b)T + b\omega^{-1}\sin(\omega T)\right)}}. \tag{20}$$

The release rate is shown in Figure 5. The response is oscillatory with an amplitude decaying as $T^{-1/2}$ which is typical of all controlled release problems with a dominant Fickian diffusion mechanism.

The pseudo-steady-state approximation suffers from two important weaknesses. First, the approximation is based on the small ϵ limit, which means that the maximum solubility of the drug is small compared with its loading. However, the case $C_s \simeq A$ occurs quite often in delivery systems involving hydrophilic polymers and drugs of high water solubility [12]. Second, the rate of the moving boundary is the controlling mechanism and the delaying effect of diffusion is ignored to first approximation. However, experiments show that the release does not follow instantaneously the changes of solubility (see, for example, Fig. 20 in [15]), which implies that the diffusion of the drug cannot be ignored. In the following section, we consider a different approximation which is based on the limit $A - C_{sm}$ small.

4. Variable solubility and loading close to solubility. In this section, we consider small values of $A - C_{sm}$ and determine a new asymptotic solution of (1)–(4). This limit $A - C_{sm} \to 0$ is equivalent to the small heat release (or high Stefan

number) limit in solidification Stefan problems [13]. To our knowledge, this limit has not been investigated in the solidification literature so we shall give a detailed analysis. The limit $A - C_{sm} \to 0$ of the exact solution in the case $F \equiv 1$ was investigated in section 2 and revealed two important points. First, $C \simeq C_{sm}$ except in the vicinity of $X = L$ where C changes rapidly from C_{sm} to 0. Second, $L - S = \sqrt{2D\alpha T}$ where $\alpha \sim -\ln(A - C_{sm})$ satisfies (9). The boundary layer problem near $X = L$ and the transcendental relation between α and $A - C_{sm}$ are two difficulties that we need to resolve as we consider the general case $C_s(T)$.

We take into account the small value of $A - C_{sm}$ by rewriting $C_s(T)$ as

$$C_s(T) = C_{sm}F(T) = C_{sm}(1 + \epsilon G(T)), \tag{21}$$

where $G(T) \leq 0$ and ϵ is a small parameter redefined as

$$\epsilon \equiv \frac{A - C_{sm}}{C_{sm}}. \tag{22}$$

Because of the moving boundary, it will be useful to reformulate the problem on a fixed interval. To this end, we introduce a new spatial coordinate defined by

$$\xi \equiv \frac{X - L}{L - S}, \tag{23}$$

which implies that the fixed and moving boundaries are now located at $\xi = 0$ and $\xi = -1$, respectively. Introducing (21) and (23) into (1)–(4) leads to the following problem for C:

$$C_{\xi\xi} = \frac{(L - S)}{D}S'\xi C_\xi + \frac{(L - S)^2}{D}C_T, \quad -1 < \xi < 0, \tag{24}$$

$$C = 0 \text{ at } \xi = 0, \tag{25}$$

$$C = C_s(T), \qquad C_\xi = \frac{(L - S)}{D}S'C_{sm}\epsilon\,(1 - G(T)) \text{ at } \xi = -1. \tag{26}$$

Note that S' appears in two places with the same term (namely, $-S'(L - S)D^{-1}$). This suggests introducing a new variable $W > 0$ defined by

$$W \equiv -\beta^{-1}\frac{L - S}{D}S'(T). \tag{27}$$

W is assumed $O(1)$ as $\epsilon \to 0$ and $\beta = \beta(\epsilon)$ is a large parameter defined implicitly by the expression

$$\epsilon = \sqrt{\frac{2}{\pi\beta}}e^{-\beta/2}. \tag{28}$$

Thus, while α is our order parameter in the special case $C_s(T) \equiv C_{sm}$ (i.e., $F(T) \equiv 1$), it plays no role here. Instead the function $\beta(\epsilon)$ defines our asymptotic sequence when $F(T)$ is arbitrary. Of course, this particular relation between ϵ and β is motivated by the special case $C_s(T) \equiv C_{sm}$ studied in section 2 in which α does play a role, and, indeed, when $F(T) \equiv 1$, $\beta \simeq \alpha$ as $\alpha \to \infty$ or, equivalently, $W \to 1$ as $\beta \to \infty$.

Furthermore, by using (51) and the fact that $T = O(\alpha^{-1})$, we note that $W = \beta^{-1}\alpha$ where α satisfies (52).

The fact that β is large implies that our basic time is the fast time

$$\overline{T} \equiv \beta T \tag{29}$$

and that the front moves on this rapid time scale. Changing variables from (ξ, T) to $(\xi, \overline{T})$ and using (27), (28), and (29), we rewrite (24)–(26) as

$$C_{\xi\xi} = -\beta W(\overline{T})\xi C_\xi + \beta W_1(\overline{T})C_{\overline{T}}, \quad -1 < \xi < 0, \tag{30}$$

$$C = 0 \text{ at } \xi = 0, \tag{31}$$

$$C = C_{sm}(1 + \sqrt{\tfrac{2}{\pi\beta}}e^{-\beta/2}G(T)) \text{ and } C_\xi = -WC_{sm}\beta\sqrt{\tfrac{2}{\pi\beta}}e^{-\beta/2}(1 - G(T)) \text{ at } \xi = -1, \tag{32}$$

where

$$W_1(\overline{T}) \equiv 2\int_0^{\overline{T}} W d\overline{T}. \tag{33}$$

The definition (33) comes from the fact that (27) can be rewritten as $W = (2\beta D)^{-1}((L-S)^2)'$, which becomes, upon integrating and using $S(0) = L$, $W_1 \equiv D^{-1}(L-S)^2 = 2\beta\int_0^T W dT$.

Both (30) and the boundary condition (32) suggest that $C \simeq C_{sm}$ except near $\xi = 0$ where we expect a boundary layer. Furthermore, we have the two basic time scales T and βT. We thus solve our equations by employing a singular perturbation technique in addition to the two time scales and using the method of matched asymptotic expansions [18].

4.1. Outer solution. Because of the exponentially small correction terms in (32), the outer solution is determined by the WKB method. Specifically, we seek a solution of the form

$$C = c_1(\beta) + \frac{e^{\beta\phi(\xi)}}{\sqrt{\beta}}\left[u_0(\xi, T) + \beta^{-1}u_1(\xi, \overline{T}, T) + \cdots\right], \tag{34}$$

$$W = 1 + \beta^{-1}w(T) + \cdots, \tag{35}$$

where $c_1(\beta)$ is an unknown constant and ϕ, u_0, $u_1, \ldots$ and w are unknown functions. In (34), we have assumed that the leading approximation does not depend on the fast time $\overline{T}$. This is suggested by the similarity solution for the constant solubility case. However, it may depend on the slow time T because the boundary conditions at $\xi = -1$ are functions of T. Introducing (34) and (35) and equating to zero the coefficients of each power of $\sqrt{\beta}$ leads to a sequence of problems for the unknowns ϕ, u_0, $u_1, \ldots$. The first two are

$$\phi' = -\xi \tag{36}$$

and

$$2\phi' u_{0\xi} + \xi u_{0\xi} + \phi'' u_0 + \xi w\phi' u_0 = 0. \tag{37}$$

Integrating (36) gives $\phi = -\xi^2/2$ and from (37) we obtain $u_0 = c_2\xi^{-1}\exp(-w\xi^2/2)$ where c_2 is a new constant of integration. Then applying the boundary conditions (32), we obtain the following leading expression of the outer solution:

$$\begin{aligned} C &= C_{sm}\left(1+\sqrt{\tfrac{2}{\pi\beta}}\exp(-\beta/2)\right) \\ &+ C_{sm}(1-G(T))\sqrt{\tfrac{2}{\pi\beta}}\exp(w/2)\tfrac{1}{\xi}\exp\left(-\tfrac{\beta}{2}\xi^2(1+\beta^{-1}w)\right). \end{aligned} \tag{38}$$

As $\xi \to 0$, the approximation (38) is clearly singular and motivates the boundary layer analysis.

4.2. Inner solution and matching conditions. We investigate the boundary layer by introducing the inner variable

$$\zeta \equiv \beta^{1/2}\xi. \tag{39}$$

With (39) and (35), we find from (30)–(32) that the leading order problem as $\beta \to \infty$ is given by

$$C_{\zeta\zeta} = -\zeta C_\zeta, \quad -\infty < \zeta < 0, \tag{40}$$

$$C = 0 \text{ at } \zeta = 0. \tag{41}$$

It admits the solution

$$C = c_3(T)\sqrt{\frac{\pi}{2}}erf(\zeta/\sqrt{2}), \tag{42}$$

where $erf(x)$ is the error function and c_3 is unknown. We obtain this coefficient from matching with the outer problem. As $\zeta \to -\infty$, (42) approaches the following limit (in terms of the outer variable ξ):

$$C \to -c_3\sqrt{\frac{\pi}{2}}\left[1+\sqrt{\frac{2}{\pi\beta}}\frac{\exp(-\frac{\beta}{2}\xi^2)}{\xi}\right]. \tag{43}$$

Now, comparing (43) and (38), matching requires the two conditions

$$-c_3\sqrt{\frac{\pi}{2}} = C_{sm} \tag{44}$$

and

$$-c_3 = C_{sm}(1-G(T))\sqrt{\frac{2}{\pi}}\exp(w/2). \tag{45}$$

Equivalently, we find c_3 and w as

$$c_3 = -C_{sm}\sqrt{\frac{2}{\pi}} \text{ and } w = -2\ln(1-G(T)). \tag{46}$$

Now using (27), (35), and the expression of w in (46), we obtain an equation for $S-L$ given by

$$(S-L)S' = \beta D\left[1+2\beta^{-1}w\right] = \beta D\left[1-2\beta^{-1}\ln(1-G(T))\right], \tag{47}$$

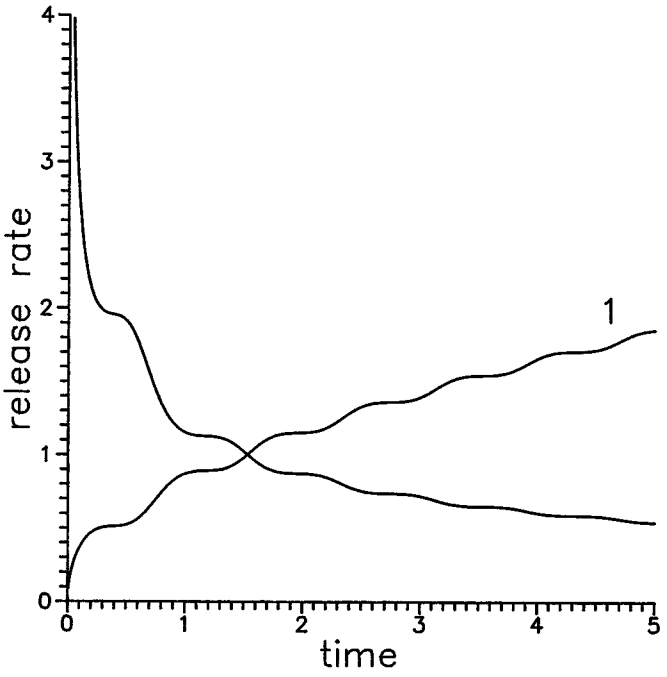

FIG. 6. *Release rate. The figure represents the release rate R divided by $A\sqrt{\frac{D\beta}{\pi}}$ as a function of time T and is given by* (49). *$G(T) = b(1-\cos(\omega T))$ where $b = -0.5$, $\omega = 8$, and $\beta^{-1} = 0.7$. Line* 1 *represents $L - S$ divided by $\sqrt{2D}$ given by* (48).

which leads to the solution

$$L - S = \sqrt{2D}\sqrt{\beta T - 2\int_0^T \ln(1 - G(T'))dT'}. \tag{48}$$

Finally, using (42) for small ζ, we determine the release rate (5) as

$$R \simeq \frac{AD}{L-S}\sqrt{\frac{2\beta}{\pi}} \simeq A\sqrt{\frac{D\beta}{\pi}}\frac{1}{\sqrt{\beta T - 2\int_0^T \ln(1-G(T'))dT'}}, \tag{49}$$

where $\beta T = O(1)$. Figure 6 illustrates this case.

5. Summary and discussion. We considered Higushi's model for controlled release of pharmaceutical drugs when the solubility at the moving boundary is a function of time. We investigated two limits of our problem which allow analytical expressions for the release rate. If $\epsilon = C_{sm}/A$ is small, the release rate R is an $O(A\sqrt{D\epsilon})$ small quantity but occurs during an $O(\epsilon^{-1})$ long time interval. On the other hand, if $\epsilon = (A - C_{sm})/C_{sm}$ is small, the release rate R is an $O(A\sqrt{D\beta})$ large quantity ($\beta \simeq \ln(\epsilon^{-2})$) but occurs during a small $O(\beta^{-1})$ time interval. Both cases are desirable for controlled drug release systems. A short but intense release rate could be interesting if the polymeric device contains a toxic drug. A third possibility which is currently tested experimentally [15] is a solubility that changes between $C_s = 0$ and $C_s \simeq A$ during short intervals of time. This problem needs to be investigated numerically, but we expect that our analysis of the case $C_s \simeq A$ will be useful in order

to estimate the order of magnitude and the time scale of the release rate during each pulse of the solubility.

Current polymeric devices successfully release drugs for prolonged periods of time using a dominant Fickian diffusion mechanism, but alternative methods of controlled release based on different mechanisms have been recently proposed. Particularly promising in this regard are biodegradable polymers which release drugs by erosion rather than diffusion [10], [15] and swelling polymers which exhibit a dominant viscoelastic effect [8]. This has led to more complicated formulations of Higushi's moving boundary problem which depend on more parameters and which do not admit exact analytical solutions [7], [16]. Numerical studies of these new models indicate changing time histories for the moving boundary, but systematic studies are still needed to fully understand the role of each parameter. In this paper, we have proposed an alternative to numerical simulations consisting of investigating two asymptotic limits. The first limit corresponds to the well-known pseudo-steady-state approximation, but the second limit has never been investigated because of the mathematical difficulties.

6. Appendix. If $F(T) = 1$, (1)–(4) represent a one-phase Stefan problem [17] which admits the similarity solution [6], [7]

$$C = \frac{C_{sm}}{erf(\sqrt{\alpha/2})} erf\left(\sqrt{\alpha/2}\left(\frac{L-X}{L-S}\right)\right), \tag{50}$$

$$S(T) = L - \sqrt{2D\alpha T}, \tag{51}$$

where $erf(x)$ is the error function [14] and α is a constant satisfying the condition

$$\frac{A - C_{sm}}{C_{sm}} = \sqrt{\frac{2}{\pi\alpha}} \exp(-\alpha/2) \frac{1}{erf\left(\sqrt{\alpha/2}\right)}. \tag{52}$$

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